REVIEW

Current challenges in the treatment of complicated urinary tract infections and prostatitis

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ABSTRACT

Serious urinary tract infections (UTIs) and acute bacterial prostatitis in adults cause significant morbidity and economic burden. Chronic bacterial prostatitis is a rather rare condition seen in urological practice, however, in certain occasions difficult to treat. In this paper, we review the bacterial etiologies and the resistance patterns found in adults with serious UTIs and bacterial prostatitis, and discuss considerations for selecting optimal antimicrobial therapy. The role of fluoroquinolones as targeted therapy for serious UTIs is highlighted. The use of effective antimicrobial therapy is the foundation of management of serious UTIs and bacterial prostatitis. Selection of the optimal antimicrobial agent must take into account patient-specific factors; infection characteristics (e.g., severity, community- vs. institutional- or hospital-acquired, need for IV agent, UTI, prostatitis); local resistance pattern; pharmacokinetic and pharmacodynamic principles; and cost. Fluoroquinolones are among the alternatives for empirical antibiotic treatment of serious UTIs and acute bacterial prostatitis. In serious UTIs activity of the antimicrobial agent against *Pseudomonas aeruginosa* needs to be taken into account. In chronic bacterial prostatitis fluoroquinolones are the first choice because of their favourable pharmacokinetic properties at the site of infection.Targeted antimicrobial therapy – emphasising the correct antibacterial spectrum and correct dosage – is likely to provide important benefits, such as reduced morbidity and associated costs, reduced emergence of resistance and maintenance of class efficacy.

Keywords Bacterial prostatitis, complicated UTIs, fluoroquinolones, hospital-acquired UTIs, pharmacodynamics, resistance rates of uropathogens, review, targeted antimicrobial therapy

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INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent microbial diseases, and their financial burden on society is substantial.

In the United States, UTIs are responsible for over 7 million physician visits annually, including more than 2 million visits for cystitis [1,2]. Approximately 15% of all community-prescribed antibiotics in the United States are dispensed for UTI, at an estimated annual cost of over $1 billion [3]. Furthermore, the direct and indirect costs associated with community-acquired UTIs in the United States alone exceed an estimated $1.6 billion [2].

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UTIs account for more than 100 000 hospital admissions annually, most often for pyelonephritis [1,2], and they also account for at least 40% of all hospital-acquired infections and are in the majority of catheter-associated cases [4–6]. Nosocomial bacteriuria develops in up to 25% of patients requiring a urinary catheter for ≥ 7 days, with a daily risk of 5% [6]. It has been estimated that an episode of nosocomial bacteriuria adds $500 to $1000 [7] to the direct cost of acute-care hospitalisation. In addition the pathogens are fully exposed to the nosocomial environment, including selective pressure by antibiotic or antiseptic substances. Therefore nosocomial UTIs comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens [6].

Whereas community-acquired UTIs are often uncomplicated, almost all nosocomial UTIs are complicated infections. Complicated UTI is a very heterogenous entity, with a common pattern of the following complicating factors:

Anatomical, structural or functional alterations of the urinary tract (e.g., stents, urine transport disturbances, instrumentation of the urinary tract, stones, tumours, neurological disorders);
Impaired renal function, by parenchymal diseases, or pre-, intra- or post-renal nephropathies (e.g., acute, chronic renal insufficiencies, heart insufficiency);
Accompanying diseases that impair the patients immune status (e.g., diabetes mellitus, liver insufficiency, immunosuppression, cancer, AIDS, hypothermia).

For antimicrobial chemotherapy the bacterial spectrum, its antimicrobial resistance patterns and the development of both over time are critical for effective chemotherapy.

The bacterial spectrum of complicated, nosocomial UTI is heterogenous and comprises a wide range of Gram-negative and Gram-positive species. The bacterial spectrum can vary geographically, over time and among units even at the same institution.

Table 1 shows the bacterial spectrum of nosocomial UTI from four different studies: North-America (SENTRY study), Europe (ESGNI-003 study), urological patients in Europe (PEP-study), and hospitalised urological patients in Straubing, Germany. In general, Gram-negative species account for approximately 70–80% of the spectrum and comprise *Escherichia coli*, followed by *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp. and *Citrobacter* spp. The Gram-positive pathogens account for about 15–30% of the spectrum and comprise enterococci, followed by staphylococci [8–13].

The prostatitis syndrome is one of the most common entities encountered in urologic practice. Classification of the prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion (EPS), and the presence or absence of bacteria in the EPS [14]. Depending on the duration of symptoms, prostatitis is described as either acute or, where symptoms are present for at least 3 months, chronic. We refer to the classification of the prostatitis syndrome suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/National Institutes of Health (NIH), in which bacterial prostatitis (acute and chronic) is distinguished from chronic pelvic pain syndrome (CPPS) [15].

The Enterobacteriaceae, in particular *E. coli*, are the predominant pathogens in bacterial prostatitis

Table 1. Bacterial spectrum of nosocomial uropathogens (≥ 2%) causing complicated UTIs, from distinct surveillance studies

Name of study	SENTRY [10]	ESGNI-003 [11]	PEP-study [13]	Straubing [12]
Regions of the world	North America	Europe	Europe	Germany
Year of surveillance	1998	2000	2003	2001
Type of surveillance	Longitudinal	Cross-section	Cross-section	Longitudinal
Origin of samples	Different departments in the hospital	Different departments in the hospital	Urology departments	Urology department
Number of pathogens (*n*)	1510	607	320	479
Species percentage				
Escherichia coli	47%	36%	35%	41%
Klebsiella spp.	11%	8%	10%	7%
Pseudomonas spp.	8%	7%	13%	6%
Proteus spp.	5%	8%	7%	9%
Enterobacter spp.	4%	4%	3%	3%
Citrobacter spp.	3%	2%	n.r.	3%
Enterococcus spp.	13%	16%	9%	18%
Staphylococcus spp.	6%	4%	4%	14%
Resistance rates of antibiotics percentage				
Ampicillin	n.r.	66%[a]	51%	47%
Ampicillin + BLI	n.r.	29%[a]	30%	30%
Trimethoprim/sulfamethoxazole	n.r.	32%[a]	45%	22%
Ciprofloxacin	3–40%[b]	17%[b]	34%	24%
Gentamicin	n.r.	18%	34%	28%
Ceftazidime	14%[c]	13%[c]	17%	28%
Amikacin	2%[c]	19%[c]	14%	n.r.
Piperacillin/Tazobactam	8%[c]	n.r.	15%	8%
Imipenem	9%[c]	14%[c]	7%	n.r.
Vancomycin	5%[d]	1%[d]	n.r.	0%[d]

BLI, β-lactamase-inhibitors; n.r., not reported; [a]Gram-negative bacteria excluding *Pseudomonas aeruginosa*; [b]Gram-negative bacteria; [c]*Pseudonmonas aeruginosa*; [d]*Enterococcus* spp.

(acute and chronic) [16], but to a lesser extent other uropathogens are also found, e.g., *Pseudomonas aeruginosa* and enterococci. The significance of intracellular bacteria, such as *Chlamydia trachomatis, Mycoplasmas* and *Ureaplasmas*, is debatable. In patients with systemic granulomatous infections or immune deficiencies, prostatitis may be caused by fastidious pathogens such as *Mycobacterium tuberculosis* or *Candida* spp., or by rare pathogens such as *Coccidioides immitis*, *Blastomyces dermatitidis* and *Histoplasma capsulatum* [17]. Depending on the geographic region, otherwise rarely cultured pathogens, e.g., *Brucella* spp., can also play a role.

RESISTANCE OF UROPATHOGENS

It is well recognised that, over the last several decades, antimicrobial resistance has evolved in uropathogens responsible for complicated UTIs and bacterial prostatitis.

Not unexpectedly, patients who experience a complicated or hospital-acquired UTI are more likely to harbour multiresistant pathogens than patients with acute uncomplicated episodes. Part of the explanation for this is that *E. coli*, a traditionally highly susceptible organism, only accounts for approximately half of infections in patients with complicated or hospital-acquired UTIs [18–20]. Moreover, recurrent *E. coli* infections are more likely to be caused by a highly resistant strain [20]. The remaining plethora of uropathogens acquired from patients with complicated UTIs or from within institutions tends to involve more difficult-to-treat Gram-negative bacilli and Gram-positive cocci.

ANTIBIOTIC RESISTANCE IN COMPLICATED, NOSOCOMIALLY ACQUIRED UTI

Nosocomial uropathogens are frequently subject to antibiotic pressure and cross-infection. The influence of these parameters can vary among regions and medical specialities. Different species of uropathogens show distinct abilities to elaborate antibiotic resistance. Table 1 shows the resistance rates of uropathogens in four surveillance studies [10–13].

If the total bacterial spectrum is considered, the aminopenicillins (with β-lactamase inhibitors) showed resistance rates of approximately 60% (respectively, 30%). Trimethoprim/sulfamethoxazole showed resistance rates between 22 and 45%. Resistance to ciprofloxacin was approximately 20–40%; to gentamicin 18–34%; to ceftazidime 13–28%; to piperacillin/tazobactam 8–15%; to imipenem 7–14%,; and resistance of enterococci to vancomycin was between 0 and 5%.

In all the studies increasing resistance rates were found with respect to specific species, e.g., *E. coli*, but not with all uropathogens. In particular, species e.g., *P. aeruginosa*, *Klebsiella, Enterobacter*, enterococci and coagulase negative staphylococci became resistant to multiple antibiotic classes and substances. However, resistance rates may vary substantially among regions. Therefore local, hospital-based surveillance of the bacterial spectrum and antibiotic sensitivity is paramount for a rational empirical therapy. Severe infections have lower mortality rates when the empirical therapy has initially covered all causative bacteria [21,22], which has been shown for bacteremic UTIs as well [23].

Table 2 shows results from continuous surveillance (1994–2004) of ciprofloxacin resistance in uropathogens isolated from hospitalised urological patients. Especially in *E. coli*, a steady increase from 4% to approximately 12% was noted.

The activity of fluoroquinolones against uropathogens obtained from patients residing in Germany with complicated or hospital-acquired UTIs [24] is shown in Table 3. Specifically, the MICs of ciprofloxacin, ofloxacin, trovafloxacin, gemifloxacin, gatifloxacin, and moxifloxacin were determined for 400 uropathogens. The most commonly isolated strains included *E. coli* and enterococci, followed by *P. aeruginosa*, *Proteus mirabilis, Klebsiella* spp. and staphylococci. Although in that study fluoroquinolone resistance in uropathogens was still low, the phenomenon of parallel susceptibility and resistance with this antibiotic class can be seen. In general, ciprofloxacin had the lowest MIC values among the Gram-negative pathogens, whereas gemifloxacin had the lowest MIC values among Gram-positive pathogens.

ANTIMICROBIAL TREATMENT OPTIONS

General Considerations

The use of effective antimicrobial therapy is the foundation of management of serious UTIs and

Table 2. Surveillance of ciprofloxacin resistance (%) in uropathogens isolated from urological hospitalised patients (1994–2004; resistant = MIC ≥ 4 mg/L) (Urologic Clinic, Hospital St. Elisabeth, Straubing, Germany).

pathogens year	*S.aureus* n/N (%)	CNS n/N (%)	*Enterococcus spp.* n/N (%)	*E. coli* n/N (%)	*Klebsiella spp.* n/N (%)	*Proteus spp.* n/N (%)	*Enterobacter spp.* n/N (%)	*Citrobacter spp.* n/N (%)	*Pseudomonas spp.* n/N (%)
1994	5/19 (26.3%)	28/40 (70%)	31/92 (33.7%)	5/114 (4.4%)	1/25 (4%)	1/32 (3.1%)	2/22 (9.1%)	5/15 (33.3%)	29/57 (50.9%)
1995	1/13 (7.7%)	37/58 (63.8%)	32/93 (34.4%)	4/107 (3.7%)	0/25 (0%)	1/21 (4.8%)	1/24 (4.2%)	2/11 (18.2%)	25/59 (42.2%)
1996	0/11 (0%)	24/34 (70.6%)	28/83 (33.7%)	2/103 (1.9%)	0/28 (0%)	2/27 (7.4%)	0/12 (0%)	0/5 (0%)	18/39 (46.2%)
1997	4/9 (44.4%)	23/46 (50%)	23/62 (37.1%)	6/113 (5.3%)	1/26 (3.8%)	2/29 (6.9%)	0/14(0%)	0/12 (0%)	17/43 (39.5%)
1998	3/14(21.4%)	33/51 (64.7%)	31/84 (36.9%)	9/104 (8.7%)	1/25 (4%)	0/22 (0%)	0/18 (0%)	2/9 (22.2%)	16/46 (34.8%)
1999	2/7 (28.6%)	23/42 (54.8%)	27/80 (33.8%)	12/128 (9.4%)	0/27 (0%)	0/23 (0%)	1/14(7.1%)	1/10 (10%)	12/39 (30.8%)
2000	1/13 (7.7%)	33/47 (70.2%)	65/138 (47.1%)	18/174 (10.3%)	1/52(1.9%)	5/43 (11.6%)	0/13 (0%)	1/7 (14.3%)	22/64 (34.4%)
2001	3/22(13.6%)	30/52 (57.7%)	55/120 (45.8%)	15/163 (9.2%)	0/38 (0%)	3/46(6.5%)	2/26 (7.7%)	0/13 (0%)	12/37 (32.4%)
2002	4/15 (26,7%)	28/49 (57,1%)	38/99 (38,4%)	25/197 (12,7%)	1/28 (3,6%)	0/32 (0%)	1/24 (4,2%)	2/13 (15,4%)	18/44 (40,9%)
2003	9/26 (34,6%)	16/38 (42,1%)	26/82 (31,7%)	21/192 (10,9%)	1/31 (3,2%)	1/40 (2,5%)	1/16(6,3%)	3/14 (21,4%)	3/27 (11,1%)
2004	7/23 (30,4%)	22/43 (51,2%)	24/75 (32,0%)	16/154 (10,4%)	1/26 (3.8%)	0/31 (0%)	2/16 (12,5%)	1/12 (8,3%)	4/30 (13,3%)

bacterial prostatitis. Selection of the optimal antimicrobial agent must take into account: patient-specific factors (e.g., history of allergy, renal function, concomitant medications); infection characteristics (e.g., severity, community- vs. institutional- or hospital-acquired, need for IV agent); local resistance patterns; pharmacokinetic and pharmacodynamic characteristics; and cost. It is important to stress that culture and susceptibility testing in patients with complicated UTIs and bacterial prostatitis is not optional [25]. In severe complicated UTI and/or pyelonephritis and in acute bacterial prostatitis empirical therapy has to be based on the local resistance pattern, but treatment should be adapted according to susceptibility testing. In mild to moderate complicated UTI and in chronic bacterial prostatitis antimicrobial therapy may not be initiated until testing results are available. Patients with symptoms of chronic prostatitis must undergo some form of quantitative segmental bacteriological localisation cultures, such as the 4-glass test described by Meares and Stamey or the 2-glass test described by Nickel [26,27].

There are many intravenous and oral antimicrobial treatment options for patients with serious UTIs (Table 4) [18,19,28–30]. Many patients with serious episodes of complicated UTI or acute prostatitis, including most hospital-acquired infections, require initial intravenous therapy because of the possibility of bacteremia or sepsis, or because of an impaired gastrointestinal tract (e.g., vomiting) that does not permit reliable absorption [28]. In addition, many experts agree that empirical therapy for the institutionalised or hospitalised patient with a serious UTI should start with an intravenous antipseudomonal agent [19,28]. Broadspectrum antimicrobial therapy including antipseudomonal activity should be considered for patients who have failed to respond after several days of therapy with more narrow spectrum agents (Table 4) [29,30]. For many years, aminoglycoside therapy, with or without ampicillin for enterococcal coverage, was a frequently recommended option for patients with normal renal function. The ability to prescribe all aminoglycosides in once-daily doses has made this class of compounds more attractive recently [31]. However, the risk of nephrotoxicity and ototoxicity remains a concern with aminoglycoside therapy and the need for routine serum monitoring increases the overall expense.

Table 3. Minimal inhibitory concentrations (MICs, mg/L) of ciprofloxacin, levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin

Pathogen	*n*	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Escherichia coli																
Ciprofloxacin	84	3	56	20	2		3									
Levofloxacin	84		4	53	22	2		3								
Gatifloxacin	84		35	41	5		3									
Gemifloxacin	70	25	42	1	1	1										
Moxifloxacin	84		4	48	29		3									
Klebsiella spp.																
Ciprofloxacin	13	1	4	4	3	1										
Levofloxacin	13			1	11		1									
Gatifloxacin	13		1	5	7											
Gemifloxacin	6		2	4												
Moxifloxacin	13			1	11		1									
Proteus mirabilis																
Ciprofloxacin	27		1	16	9	1										
Levofloxacin	27			1	14	11	1									
Gatifloxacin	27		1	3	19	4										
Gemifloxacin	27			1		10	16									
Moxifloxacin	27				2	2	20	3								
Enterobacter spp.																
Ciprofloxacin	6	1	2	2	1											
Levofloxacin	6			4		2										
Gatifloxacin	14		3	2	3	3	3									
Gemifloxacin	9		1	2	1	1	2	1	1							
Moxifloxacin	14		2	2	3	4	1	1	1							
Pseudomonas aeruginosa																
Ciprofloxacin	48				1	12	15	6	2		1		1	4	6	
Levofloxacin	48						2	22	7	5		1		2		9
Gatifloxacin	48							17	11	5	4			5	6	
Gemifloxacin	45						12	16	6	2				1	8	
Moxifloxacin	48							5	20	8	4				10	1
Staphylococcus aureus																
Ciprofloxacin	28					1	3	13	4	1			1		3	2
Levofloxacin	28					4	14	4			1		3	2		
Gatifloxacin	28			1	11	6	4			1	5					
Gemifloxacin	27		5	10	3	2	1		1		3	2				
Moxifloxacin	28		3	10	7	2			1		5					
CNS																
Ciprofloxacin	57					2	21	5	5			1	3	3	5	12
Levofloxacin	57					5	23	5			2	7	7	6	1	1
Gatifloxacin	57				7	22	4			15	5	2	2			
Gemifloxacin	56	1	5	22	2	2	1		4	6	7	4	1	1		
Moxifloxacin	57			15	14	4		1	5	11	3	4				
Enterococci																
Ciprofloxacin	126							2	18	79	3	1	1		14	8
Levofloxacin	126				1			1	12	85	4	1		6	12	4
Gatifloxacin	126			5	73	24		1	1	8	14					
Gemifloxacin	125			4	57	40			5	11	8					
Moxifloxacin	126				2	31	69			1	5	11	7			

CNS, coagulase-negative staphylococci.

Numerous other parenteral options are available for treatment of serious UTIs and acute prostatitis, including extended-spectrum β-lactams (β-lactam/β-lactamase inhibitor combinations, imipenem, advanced-generation cephalosporins) and fluoroquinolones (Table 4). The optimal agent should have adequate coverage against *P. aeruginosa*, especially for intensive care unit patients and for those with urosepsis. While β-lactam antimicrobials are generally well-tolerated, care must be taken to avoid their use in patients with a history of hypersensitivity.

Following definitive identification of the causative pathogen and susceptibility testing, therapy may need to be modified. The total duration of therapy is longer for patients with complicated or hospital-acquired UTIs (7–14 days) and patients with bacterial prostatitis (acute 2–4 weeks, chronic 4–6 weeks) compared with uncomplicated episodes (e.g., 3 days). Patients who respond adequately to initial intravenous therapy and who have a normally functioning gastrointestinal tract can be switched to oral therapy as soon as possible.

Pharmacokinetic and pharmacodynamic considerations in patients with complicated UTI

Adequate treatment of UTI depends on the antimicrobial being able to inhibit the growth or to kill bacteria present in the urinary tract. Accordingly, antimicrobials that are primarily

Table 4. Recommendations for the empirical antibiotic therapy of UTI (modified from Naber *et al.*, 2001 [30])

Diagnosis	Frequent uropathogens	Empirical initial therapy	Duration of therapy
UTI	*Escherichia coli*	Fluoroquinolone	At least 3–5 days after defervescence, respectively, removal of the complicating factor
Complicated nosocomial UTI	*Enterococci*	Aminopenicillin/BLI	
Pyelonephritis acute, complicated	*Pseudomonas* spp.	Cefotaxime, ceftriaxone	
	Staphylococci	Ertapenem	2–3 days after defervescence in patients with indwelling catheters
	Klebsiella spp.	If initial therapy fails after 1–2 days:	
	Proteus spp.	Piperacillin/tazobactam	
	Enterobacter spp.	Ceftazidime, cefepime	
	other Enterobacteria	Imipenem, meropenem	
	(*Candida* spp.)	In case of *Candida* spp.: Fluconazole Voriconazole Caspofungin Amphotericin B	
Prostatitis-acute	*Escherichia coli*	Ciprofloxacin, levofloxacin, gatifloxacin[a], moxifloxacin[a]	2–4 weeks
	Enterococci	Aminopenicillin/BLI	
	Pseudomonas spp.	Cefotaxime, ceftriaxone	
	Staphylococci	Ertapenem	
	Klebsiella spp.	If initial therapy fails after 1–2 days:	
	Proteus spp.	Piperacillin/tazobactam	
	Enterobacter spp.	Ceftazidime, cefepime	
	other Enterobacteria	Imipenem, meropenem	
Prostatitis chronic, bacterial		Ciprofloxacin, levofloxacin, gatifloxacin[a], moxifloxacin[a]	4–6 weeks

BLI, β-lactamase inhibitor.

eliminated via renal excretion and achieve high urinary concentrations (100–1000 times concomitant serum concentrations) (e.g., ampicillin/sulbactam, cefuroxime, gatifloxacin, levofloxacin), theoretically represent optimal choices for the treatment of UTIs. But besides favourable pharmacokinetics, an agent suitable for the treatment of severe complicated UTI should also provide optimal pharmacodynamic properties at the site of infection, i.e., urinary bactericidal activity. Thus, even for agents modestly eliminated by renal mechanisms but with high intrinsic potency (MIC) against the most common uropathogens (e.g., ciprofloxacin), there are also important considerations in antimicrobial selection [32]. Agents whose antibacterial activity are compromised by changes in urinary pH may not be the best choices for patients with serious UTIs. If infection involves renal tissues or the patient has urosepsis, antimicrobial concentrations must exceed the MIC for the infecting pathogen to produce the desired outcome. As such, adequate serum concentrations are necessary to produce high tissue concentrations, thereby necessitating administration of high dose intravenous antimicrobials.

While pharmacodynamic studies in UTI are relatively scarce, at least one recent study has documented that therapeutic success following β-lactam therapy depends on the time the antimicrobial concentration remains above the MIC (T > MIC). A recent data analysis by Frimodt-Møller reported that there was a significant correlation between the cumulative T > MIC and bacteriological cure, wherein a cumulative T > MIC of 30% or more of the 24 h dosage provided a maximal cure rate of 80–90% [33]. The authors postulated that the reason β-lactams often have not provided successful outcomes in the treatment of UTIs, compared with other antimicrobial classes, is most likely improper dosing (i.e., dose too low and infrequent dosage interval).

For drugs with concentration dependent time-kill activity, such as the aminoglycosides and the fluoroquinolones, a positive outcome appears to be more dependent on the C_{max}/MIC or AUC/MIC ratio. While it remains unclear which ratio is a better predictor of outcome, in either case a high ratio is desirable. The pharmacodynamics of ciprofloxacin were investigated in one animal model UTI study in mice infected with *E. coli* [33]. While data were limited to three points, there was an obvious correlation between reduced bacterial counts and the AUC/MIC ratio. Despite the paucity of pharmacodynamic data to guide therapy of UTIs, it has been noted that among the available quinolones, the C_{max}/MIC and AUC/MIC ratios are highest for ciprofloxacin against

P. aeruginosa [34]. For other Gram-negative infections, the pharmacodynamic properties are more similar among the available quinolone agents. This model was unable to evaluate the aminoglycosides using pharmacodynamic principles because these agents are characterised by high binding to the renal cortex [33].

Severe UTIs, however, are a combination of tissue infection and urine infection. A significant part of the bacteria (sometimes more than 10^6/mL) is found free in the bladder lumen. Therefore a high urinary excretion of the antibiotic is also needed. The urinary concentration, however, has to be correlated with the respective antibacterial activities. This can be done, for example, in an ex-vivo model by determining the urinary bactericidal titres (UBT). In this model pharmacokinetic and pharmacodynamic parameters of an antibiotic in urine are linked together. Various fluoroquinolones have been compared with each other in this way, showing that the urinary concentrations (after an oral single dose of 500 mg ciprofloxacin, 400 mg enoxacin and 400 mg norfloxacin) were highest with enoxacin, followed by ciprofloxacin and norfloxacin. The determination of the UBTs against susceptible Gram-positve and -negative uropathogens, however, showed that the activity of ciprofloxacin was twice that of enoxacin and twice that of norfloxacin [32]. Therefore, one dose of ciprofloxacin is comparable to two doses of enoxacin or four doses of norfloxacin, in order to achieve comparable UBTs. In similar investigations ciprofloxacin was compared with levofloxacin and gatifloxacin [35]. If these results are summarised and compared with the data of clinical studies, equivalent dosages for oral fluoroquinolones can be detemined.

Appropriate dosing is especially important to minimise the development of resistance and to maintain antimicrobial efficacy. For patients with serious UTIs, higher than approved doses may be needed, especially against difficult-to-treat pathogens such as *P. aeruginosa* [32]. For example, intravenous or oral ciprofloxacin 750 mg twice-daily or levofloxacin 500 mg twice-daily may be more appropriate than conventional dosing.

Pharmacokinetic and pharmacodynamic considerations in patients with acute or chronic prostatitis

The drug penetration in the prostate tissue is supposedly a passive transport mechanism involving of diffusion and concentration [36]. The drug characteristics that determine simple diffusion are concentration, lipid solubility, degree of ionisation (biological membranes do not allow the passage of charged substances), degree of protein binding, and the size and shape of the molecule (small water-soluble molecules can cross biological membranes as part of the free water diffusion). The presence of a pH gradient across a biological membrane introduces the phenomenon of ion trapping. In a stable system the uncharged fraction of a lipid-soluble drug equilibrates on the two sides of the membrane, but the charged fraction is greater on one side or the other, depending on the pH. The greatest drug concentration (sum of charged and uncharged fractions) is on the side with the higher degree of ionisation. Thus, a weak base, as in trimethoprim with a pKa of 7.4, will be concentrated in an acidic prostatic fluid as found in dogs [37], but not in an alkaline mileu, such as seminal fluid. The pH of prostatic fluid in patients with chronic bacterial prostatitis is also often alkaline; thus concentrations in prostatic secretion may be inadequate [38,39].

The fluoroquinolones in clinical use are neither pure acids nor bases but have characteristics of both, i.e., amphoteric or zwitter-ionic drugs [40,41]. Most quinolones that are amphoteric drugs have two ionising groups, one positively and one negatively charged, and thus two pK_a values [41]. At one pH value, which is between the two pK_a values and is different for each amphoteric drug, the amount of charged drug is minimal (isoelectric point). At higher and lower pH values more drug is charged. Since the highest drug concentration occurs on the side with the higher degree of ionisation, drugs with an isoelectric point close to plasma pH should concentrate in fluids with a pH above and below plasma pH. This allows prostatic fluid levels that compare favourably with plasma levels, with ratios ranging from 0.12 to 1.02 (Table 5) [42–45]. The concentration of some fluoroquinolones in the alkaline seminal fluid may even exceed that in plasma (Table 5). Macrolides also penetrate into prostatic and seminal fluids very well [36,46]. Although it remains unproven clinically, considerable evidence suggests that bacteria in prostatic tissue survive in a milieu protected by biofilms [47].

The reason for the administration of antibiotics for chronic pelvic pain syndrome (CPPS) with inflammation (NIH category IIIA), in which no

Table 5. Concentrations of fluoroquinolones in prostatic and seminal fluids (in case of split ejaculation, portion 2) of volunteers 2–4 h after drug administration [42–45]

Concentrations of Fluoroquinolones in Prostatic and Seminal Fluids

Quinolone	Dose (mg)	Median plasma concentration (mg/L)	Median prostatic fluid concentration (mg/L)	Median ratio of prostatic/plasma drug concentrations	Median seminal fluid concentration (mg/L)	Median ratio of seminal/plasma drug concentrations
Norfloxacin	800 PO	1.40	0.14	0.12	n.d.	–
Ciprofloxacin	200 IV	0.44	0.08	0.18	2.53	7.1
	750 PO	0.88	0.23	0.23	6.57	7.7
Fleroxacin	400 PO	3.71	1.00	0.28	5.80	1.7
Ofloxacin	400 PO	2.00	0.66	0.33	4.09	4.0
Enoxacin	400 PO	1.09	0.39	0.39	2.19	2.2
	428 IV	1.26	0.57	0.47	3.50	2.8
Lomefloxacin	400 PO	1.81	1.38	0.48	2.04	1.3
Gatifloxacin	400 PO	1.92	1.03	1.02	1.75	1.0

n.d., not done.

pathogens can actually be cultured, is that there may be a bacterial infection even though bacteria are not detected by conventional methods. However, by using a 16S rDNA assay, bacterial DNA sequences could be detected in a high rate in patients with CPPS [48]. Furthermore, clinical studies report the positive effects of antibiotics in inflammatory CPPS [49,50]. Antimicrobial therapy *ex juvantibus* is therefore justified. An oral fluoroquinolone should be given for 2–4 weeks after the initial diagnosis. The patient should be reassessed and antibiotics continued only if the patient reports a positive effect of the treatment in terms of pain relief. A total treatment period of 4–6 weeks is then recommended [51]. Table 6 shows a possible algorithm for the treatment of prostatitis syndrome.

FLUOROQUINOLONE CLINICAL STUDIES IN PATIENTS WITH COMPLICATED UTI

A limited number of US and international clinical trials have been published, and provide evidence to support the effectiveness of the fluoroquinolones in the treatment of complicated and hospital-acquired UTIs [52–75]. However, the findings of these trials are often difficult to compare or interpret because of differing or incomplete definitions of the 'complicated' aspect. Although these trials vary in their study design, many support the use of fluoroquinolones in the treatment of serious or complicated UTIs; the most experience has been garnered with ciprofloxacin [52–64]. Several contemporary and key ciprofloxacin studies are described in more detail below.

The majority of the published ciprofloxacin trials on serious UTI employed the conventional twice-daily tablet [52,57–63], while one recent preliminary report demonstrated the effectiveness of a new once-daily extended-release tablet formulation [64]. Three of these studies were conducted primarily in Germany and used a relatively low dose of ciprofloxacin (250 mg twice a day), but with good outcomes [60–62]. The majority of these published clinical trials with oral ciprofloxacin reveal excellent bacteriologic (> 84%) and clinical cure rates (> 90%). As expected, all of these trials demonstrated that

Table 6. Practical recommendations for antibiotic therapy in prostatitis

Acute bacterial prostatitis-NIH category I
Quantitative segmental bacteriological localisation cultures and microscopy of EPS not indicated. Isolation of pathogen from urine.
(1) Empirical therapy with β-lactam antibiotics and/or fluoroquinolones After susceptibility testing adaptation of therapy, if needed. After clinical improvement continued antibiotic oral therapy for 4–6 weeks.
(2) In case of residual urine: < 100 mL, add α-receptor blocker > 100 mL, insert suprapubic catheter (3) In case of prostatic abscess, surgical therapy (e.g., TURP)

Inflammatory CPPS-NIH category III A
Quantitative segmental bacteriological localisation cultures and microscopy of EPS mandatory.
(1) Oral fluoroquinolone for 2–4 weeks.
(2) Reassessment of patient and continuation of antibiotics only if patient reports clinical improvement. A total treatment period of 4–6 weeks is then recommended.

Chronic bacterial prostatitis-NIH category II
Quantitative segmental bacteriological localisation cultures and microscopy of EPS mandatory.
(1) Empirical therapy with fluoroquinolones (4–8 weeks) ± α-receptor blocker (6 months)
(2) In case of recurrent infection or reinfection repeated bacteriological sampling and widended diagnostics (e.g., urodynamics), adaptation of antibiotic therapy if needed.

Non inflammatory CPPS-NIH category III B/ Asymptomatic prostatitis-NIH category IV
Quantitative segmental bacteriological localisation cultures and microscopy of EPS mandatory No consensus regarding the role of antibiotic treatment.

ciprofloxacin was at least equivalent to a comparator regimen (e.g., ofloxacin, gatifloxacin). In general, ciprofloxacin was effective for serious UTIs due to *P. aeruginosa*.

One study demonstrated that ciprofloxacin was significantly bacteriologically superior to a comparator agent in a population with long-term bladder catheterisation [52]. The bacteriologic response at the early follow-up visit (5–9 days post-therapy) demonstrated that ciprofloxacin 500 mg twice daily was superior to the aminoglycoside regimen ($p = 0.0005$) [52]. The response rates were similar between the two treatment groups at the long-term follow-up visit (28–30 days post-therapy). In this trial, 75% of *P. aeruginosa* isolates were eradicated at the short-term follow-up by both ciprofloxacin and aminoglycoside regimens, although there was a high rate of recurrence in both treatment groups. While ciprofloxacin provided superior short-term results, recurrence was high in both treatment groups, probably due to the presence of biofilms and the fact that catheters could not be removed in these patients. These findings stress the difficulty in treating patients who have permanent indwelling urinary catheters.

We evaluated the efficacy of two oral dosing regimens of gatifloxacin compared with ciprofloxacin in the treatment of complicated urinary tract infection in a randomised, double-blind multicentre trial [63]. One thousand one hundred and twenty-three adult patients with complicated UTI (70%) or pyelonephritis (30%) were initially enrolled, and 1122 were treated. Of these, 824 were included in a modified intent-to-treat (ITT) population: gatifloxacin 200 mg (274 patients) or 400 mg (280 patients) once daily or ciprofloxacin 500 mg twice daily for 5–14 days (269 patients). Bacteriological and clinical responses were assessed 7–9 days after the end of treatment (EOT) and 4–6 weeks post-treatment (end-of-study visit, EOS). The bacteriological response rates per patient at EOT in the gatifloxacin 400 mg, gatifloxacin 200 mg and ciprofloxacin groups were 77%, 78% and 73%, respectively. At EOS they were slightly lower: 70%, 71% and 69%, respectively. The clinical responses at EOT were 69%, 70% and 65%, respectively. At EOS they were 71%, 70% and 74%, respectively. The overall eradication rates of initial pathogens at EOT and EOS were 85.3% and 88.4%, respectively in the gatifloxacin 400 mg group; 84.1 and 90.1%, respectively in the gatifloxacin 200 mg group and 85.1 and 91.4%, respectively in the ciprofloxacin group. Therefore both oral regimens of gatifloxacin were as effective as that of ciprofloxacin.

A recent large, North American study was completed by Talan *et al.* wherein extended-release ciprofloxacin (1000 mg once daily) was compared with standard twice-daily ciprofloxacin 500 mg, each for 7–14 days duration for patients with complicated UTIs [64]. Of 1035 intent-to-treat patients, including some patients with acute uncomplicated pyelonephritis, a valid pretherapy pathogen was isolated in 641 patients. The MIC_{90s} for the most frequently isolated Gram-negative pathogens were: *E. coli* (0.25 mg/L), *K. pneumoniae* (0.5 mg/L), and *Proteus mirabilis* (2.0 mg/L). Overall, 49 of 1035 (4.7%) patients had ciprofloxacin-resistant (MIC ≥ 4 mg/L) uropathogens at baseline. Only patients with ciprofloxacin-susceptible isolates were subsequently evaluated for efficacy. At the test-of-cure visit (5–11 days post-therapy), bacteriologic eradication in the complicated UTI cohort was achieved in 89% of extended-release ciprofloxacin recipients vs. 81% of twice-daily ciprofloxacin recipients. Corresponding rates of clinical success were 96% and 93%, respectively. Long-term success rates were comparable between the treatment groups. The authors concluded that extended-release once-daily ciprofloxacin 1000 mg was as effective as standard twice-daily ciprofloxacin 500 mg in adults with complicated UTI.

Mombelli *et al.* investigated the efficacy of oral (500 mg twice daily) vs. intravenous ciprofloxacin (200 mg twice a day) as empirical therapy in 141 patients with community- and hospital-acquired complicated UTIs or severe pyelonephritis [56]. Only patients with severe sepsis (defined as the presence of infection-related organ dysfunction) were excluded. Resistance to ciprofloxacin was found for 11 (8%) baseline organisms, including five e*nterococcus* spp. and one each of *P. aeruginosa*, *E. coli*, *Enterobacter* spp., *Staphylococcus aureus*, coagulase negative staphyloccci, and *Candida albicans*. This study found that empirical oral ciprofloxacin was bacteriologically and clinically as effective as intravenous ciprofloxacin for management of serious UTIs, including bacteremia, in patients without severe sepsis, obstruction, or renal foci of suppuration. Rates of bacteriologic failure or unsatisfactory clinical response were extremely low (2% and 3%, respectively, for

intravenous regimes vs. 3% and 4% for oral regimes). Importantly, no infection-related deaths occurred and no patient had to be switched from empirical to alternative therapy early because of clinical worsening. However, treatment was ultimately altered following availability of susceptibility findings in 7% of those randomised to intravenous ciprofloxacin vs. 14% of oral ciprofloxacin recipients ($p = 0.31$). There are several unique aspects and findings to this trial: enrolled patients had serious UTIs, including 53 patients with proven bacteremia; males comprised over 40% of the study population and nosocomial acquisition was reported for 23%; and patients with resistant organisms were not automatically excluded. It is also noteworthy that the majority of ciprofloxacin resistance was against Gram-positive organisms and that despite this, most patients had an adequate initial clinical and bacteriologic response. In fact, clinical response to ciprofloxacin was satisfactory in six of seven patients with ciprofloxacin-resistant pathogens, including two with episodes of bacteraemia. Although this study was not large, it provides compelling evidence that both intravenous and oral ciprofloxacin are effective in the initial treatment of patients with serious UTIs, including nosocomially acquired infections.

FLUOROQUINOLONE CLINICAL STUDIES IN PATIENTS WITH CHRONIC BACTERIAL PROSTATITIS

Most studies in patients with chronic bacterial prostatitis (CBP) have not been well controlled and have been variably designed [44,76]. As a result, comparison is difficult. Duration of therapy has ranged from 14 to 150 days and follow-up investigation has not been standardised. Since relapse and reinfection are commonly observed in these patients, only the results of studies with a follow-up of at least 6 months should be taken into consideration. In this respect most experience has been gathered with ciprofloxacin [77–85]. Overall, it appears that 60–80% of patients with *E. coli* and other Enterobacteriaceae can be cured with a 4–6-week course of therapy. However, prostatitis due to *P. aeruginosa* and enterococci often fails to respond to treatment. Newer fluoroquinolones, such as levofloxacin or gatifloxacin, with improved activity against Gram-positive and so-called atypical pathogens, have not yet been tested sufficiently in suitable clinical trials [76,86]. One trial tested levofloxacin 500 mg (once daily) vs. ciprofloxacin 500 mg (twice daily) with a two-week follow-up and reported similar clinical success rates of 75% and 73%, respectively, and similar microbiologic eradication rates of 75% and 77%, respectively [87].

CURRENT APPROACH TO TREATMENT

Serious UTI and acute bacterial prostatitis episodes require immediate empirical treatment, and often hospitalisation and administration of intravenous antimicrobials, especially in the case of severe presentations (e.g., fever, vomiting) or when urosepsis is suspected. In patients with chronic bacterial prostatitis the choice of antibiotic therapy should await identification and susceptibility results. The pathogens encountered in patients with serious UTIs and acute prostatitis are unpredictable, and include non-*E. coli* Gram-negative bacteria and, to a lesser extent, Gram-positive bacteria (approximately 20%), and have a high potential for being drug-resistant [10]. Accordingly, an appropriately collected urine specimen must be obtained for culture and susceptibility testing for each serious UTI episode prior to initiating therapy. Selection of empirical antibiotic therapy must take into account current resistance patterns for common uropathogens and be individualised for a given facility, hospital ward, and community, as well as individual patient factors based on prior therapy and underlying comorbidities. Because many patients often have underlying immunosuppression (e.g., advanced age, comorbidities), potent broad-spectrum coverage directed primarily at Gram-negatives, including *P. aeruginosa*, may be needed [19,20]. The decision to initiate empirical therapy with an antipseudomonal agent remains one of clinical judgment, but may become necessary following identification of *P. aeruginosa* from an appropriately cultured urine specimen. Uropathogens causing chronic bacterial prostatitis frequently are antibiotic resistant, because patients with recurrent infections typically have undergone multiple antibiotic treatment regimens.

The selection of an optimal empirical therapy for treatment of serious UTI and acute bacterial prostatitis remains challenging for many physicians and will depend mostly on the expected bacterial

spectrum, its susceptibility profile and suitable pharmacokinetic/pharmacodynamic properties [30]. While a number of antimicrobials are indicated for treatment of complicated UTIs, the need to cover a range of Gram-negative and Gram-positive bacteria with unpredictable susceptibility patterns often confounds the therapeutic selection process. Over the last two decades, extended-spectrum β-lactam antimicrobials have shown decreased activity against common nosocomial urinary tract pathogens [10]. Furthermore, many β-lactams also lack reliable antipseudomonal coverage, making these less attractive monotherapeutic options. Fluoroquinolones provide excellent Gram-negative coverage, but with varied activity against *P. aeruginosa* and Gram-positive strains. Ciprofloxacin remains the most potent fluoroquinolone *in vitro* against *P. aeruginosa* [24,88], although resistance has risen in the two decades of its use [8,10]. For hospitalised patients with suspected pseudomonal infection, ciprofloxacin is the most logical empirical choice when susceptibility patterns for the institution warrant its use. For patients without risk factors for pseudomonal infection, other intravenous and oral fluoroquinolones, such as levofloxacin and gatifloxacin, are options. For patients who can be switched to oral therapy (e.g., those with a positive response following intravenous therapy and adequate gastrointestinal function), extended-release once-daily ciprofloxacin is an effective new option, although there are limited data concerning *P. aeruginosa* [64]. Regardless of the agent chosen, treatment of serious UTIs is typically prolonged (7–14 days) in order to ensure microbiological success and a low rate of clinical relapse [28,89,90]. Correcting the underlying urinary tract abnormalities responsible for the infection is also crucial to management of patients with complicated UTIs.

Treatment of acute bacterial prostatitis should last for 2–4 weeks to prevent development of chronic bacterial prostatitis [51]. Fluoroquinolones are the first choice of agents because of their favourable pharmacokinetics in the prostate tissue and prostatic excretions. All other antibiotic classes available (except macrolides) exhibit inferior pharmacokinetic properties in that respect [51].

CONCLUSION

Physicians have an increasing responsibility to select the most appropriate antimicrobial for treatment of all infections, including serious UTIs and bacterial prostatitis. The use of targeted therapy – emphasising the antibacterial spectrum and pharmacodynamic properties – is likely to provide important benefits, such as reduced morbidity and associated costs, reduced emergence of resistance and maintenance of class efficacy [34]. While many antimicrobial agents may be clinically effective against UTIs, the use of agents with only marginal activity against given pathogens may compromise the effectiveness of other agents in the same class and in some cases, reduce the usefulness of agents in other classes.

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